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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,976	SORENSEN ET AL.	
	Examiner	Art Unit	
	Mark Navarro	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,17,18 and 20-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,17,18 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment filed October 26, 2007 has been received and entered. Claims 12-13, 15-16, 19 and 31-41 have been cancelled. Accordingly, claims 1-11, 14, 17-18, and 20-30 are pending in the instant application.

Claim Objections

1. The objection of claims 12-15, 18-19 and 22 for containing non-elected subject matter and for being contradictory regarding SEQ ID NO: 6 is withdrawn in view of Applicants amendment.

Claim Rejections - 35 USC § 112

2. The rejection of claims 1-15, 17-24 and 29-30 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "binding member" and "N-terminal part" is withdrawn in view of Applicants amendment.

3. The rejection of claims 12-15, and 18-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained towards amended claims 1-11, 14, 17-17-18, and 20-30. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants are asserting that at least by the earliest priority date available to the instant application (7/3/03), techniques were known for producing functional homologues of binding polypeptides that would specifically bind to the same antigen as a parent binding polypeptide, without any prior knowledge of the amino acid residues in the parent binding polypeptide. Applicants cite several publications demonstrating this point: Klimka (Br. J. Cancer 83 (2000): 252-260, tech production of derivative human anti-CD30 scFv antibody from a parent murine anti-CD30 scFv antibody in which the derivative and parent antibodies share only one CDR. Marks et al (Biotechnology Vol. 10 (1992): 779-783) teach production of a derivative antibody specific for hapten 2-phenyloxazol-5-one with up to 30 fold increased affinity relative to a parent antibody which shared only one CDR. Rader et al (PNAS USA 95 (1998): 8910-8915) teach production of derivative humanized antibodies having the same or higher affinity realative to a parent mouse antibody, which approach did not consider the amino acid residues present in a parent antibody's CDR that participate in antigen binding specificity and affinity.

Applicants arguments have been fully considered but are not found to be fully persuasive.

Applicants assert that at least by the earliest priority date available to the instant application (7/3/03), techniques were known for producing functional homologues of binding polypeptides that would specifically bind to the same antigen as a parent binding polypeptide, without any prior knowledge of the amino acid residues in the parent binding polypeptide, and have cited multiple teachings to demonstrate this

principle. The prior art methods for screening rely on a two step process where each step results in an antibody, however, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody. In contrast to this approach, Applicants claims do not recite any defined sequences, rather only "functional homologues" of SEQ ID NO: 4 or SEQ ID NO: 6.

Padlan et al (PNAS (1989) 86:5938-5942) describe the crystal structure of an antibody-lysozyme complex where all 6 CDRs contribute at least one residue to binding and one residue in the framework is also in contact with the antigen.

Vajdos et al (J. Mol. Biol. (2002) 320 : 415-428) set forth that antigen binding is primarily mediated by the CDRs but more highly conserved framework segments are mainly involved in supporting CDR loop conformations and in some cases framework residues also contact antigen.

MacCallum et al (J. Mol. Biol. (1996) 262 : 732-745) analyzed many different antibodies for interaction with antigen and found that although CDR3 of the VH dominate the interaction, a number of residues outside the CDRs make antigen contacts and residues in the CDRs are important for backbone conformations.

De Pascalis et al (Journal of Immunology 2002 169: 3076-3084) teach that grafting of CDRs onto a human framework required some residues in all 6 CDRs as well as specific frameworks.

As demonstrated by the cited references above, it is unpredictable which amino acids could be removed, added or substituted, as often all 6 CDRs and even framework regions of an antibody contribute to antigen binding.

The instant claims are drawn to binding polypeptides comprising a sequence or "functional homologue" thereof. Selective point mutations to one key residue could eliminate the function of the polypeptide. It could eliminate its binding properties. If the range of decreased binding ability after single point mutations of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antibody that precipitously or progressively does not recognize the native antigen in the polyclonal pool. As stated above, Applicants have not shown which amino acids may be changed without causing a detrimental effect to the binding domain in which it represents. The claims allow for as great as 40% variation or even more, e.g., homologues of SEQ ID NO: 4 or 6. Applicants have provided no guidance to enable one of skill in the art how to determine without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be

possessed. See Mikayame et al (PNAS USA 90: 10056-10060, 1993) which teach that the three dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities.

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that a "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.)" Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Given the lack of guidance contained in the specification regarding acceptable amino acid substitutions, additions or deletions, one of skill in the art would be forced into excessive experimentation to practice the broadly claimed invention.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

4. The rejection of claims 12-15, 18 and 19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained as applied to amended claims 1-11, 14, 17-18, and 20-30.

Applicants are asserting that protein variants can meet the requirements of 35 USC 112 first paragraph, even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) if the specification provides an assay for detecting the functional activity of the protein, and (3) the variant has some sequence relationship to the original sequence.

Applicants arguments have been fully considered but are not found to be persuasive.

Applicants arguments are not found to be persuasive in view of the teachings set forth above. Each of Padlan et al, Vajdos et al, MacCallum et al, and De Pascalis et al teach that grafting of CDRs onto a human framework often required some residues in all 6 CDRs as well as specific frameworks. Consequently, the procedures for creating variant proteins when starting only with a "functional homologue" of SEQ ID NO: 4 or 6 is far from routine.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The specification does not

"clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."

Applicant is reminded that Vas-Cath make clear that the written description provision of 35 USC 112 is severable from its enablement provision.

Furthermore, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

No disclosure, beyond the mere mention of variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. The rejection of claims 1-5, 10-11, 14, 17-18, and 20-23 under 35 U.S.C. 102(b) as being anticipated by Korman et al in light of Hoogenboom is maintained.

Applicants are asserting that the cited art does not disclose of SEQ ID NO: 4 or any functional homologue thereof.

Applicants arguments have been fully considered but are not found to be fully persuasive.

As set forth previously, Korman et al disclose of an isolated binding domain which is 100% identical to Applicants binding domain comprising SEQ ID NO: 6. Furthermore, the isolated binding domain disclosed by Korman et al is an antibody, which inherently will contain six CDR (binding domains). Applicants have offered no explanation as to why none of the other five CDRs disclosed by Korman fall outside the scope of "functional homologue" of SEQ ID NO: 4. The Examiner agrees that Korman et al do not disclose of a CDR comprising SEQ ID NO: 4, however the claims are not so limited, each of the other five CDRs disclosed by Korman et al are reasonably deemed to be functional homologues since they share some level of percent identity with SEQ ID NO: 4 and can be therefore considered functional homologues.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

6. The rejection of claims 1-7, and 17 under 35 U.S.C. 102(b) as being anticipated by Crook et al in light of Hoogenboom is maintained.

Applicants assertions are identical to those recited above in paragraph number 5 and have been fully addressed in paragraph number five.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

7. The rejection of claims 1-7, 10, and 22 under 35 U.S.C. 102(b) as being anticipated by Srivastava et al in light of Hoogenboom is maintained.

Applicants assertions are identical to those recited above in paragraph number 5 and have been fully addressed in paragraph number five.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

8. The rejection of claims 6, 7, 24, 29 and 30 under 35 U.S.C. 102(b) as being anticipated by Gor et al in light of Hoogenboom is maintained.

Applicants assertions are identical to those recited above in paragraph number 5 and have been fully addressed in paragraph number five.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The rejection of claims 6-9, 20-21 and 23 under 35 U.S.C. 103(a) as being unpatentable over Srivastava et al or Korman et al in view of Kriangkum et al and Hoogenboom is maintained.

Applicants assertions are identical to those recited above in paragraph number 5 and have been fully addressed in paragraph number five.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

The following new ground of rejection is applied to the amended claims:

Claim Objections

10. Claim 14 is objected to because of the following informalities: Claim 14 is listed as an original claim, however the entire claim has been struck through. Appropriate correction is required.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro whose telephone number is (571) 272-0861.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shannon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Navarro
Primary Examiner
January 6, 2008